GP/1623 #5
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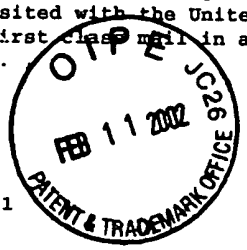

John P. Parise
(Print Name)

(Signature)

Date: December 14, 2001

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Pierre Barbier, et al.

Serial No.: 09/912,957

Filed: July 25, 2001

For: **ORLISTAT COMPOSITIONS**

Group No.: 1623

TRANSMITTAL OF CERTIFIED COPY

December 14, 2001

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country	Application No.	Filing Date
Europe	00116393.0	July 28, 2000

Respectfully submitted,

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Bescheinigung Certificate Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

00116393.0

Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.:
Demande n°: 00116393.0

Anmeldetag:
Date of filing:
Date de dépôt: 28/07/00

Anmelder:
Applicant(s):
Demandeur(s):
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Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
New pharmaceutical composition

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat: State: Pays:	Tag: Date: Date:	Aktenzeichen: File no. Numéro de dépôt:

Internationale Patentklassifikation:
International Patent classification:
Classification internationale des brevets:
/

Am Anmeldetag benannte Vertragstaaten:
Contracting states designated at date of filing: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE/TR
Etats contractants désignés lors du dépôt:

Bemerkungen:
Remarks:
Remarques:

EXAMPLES

Example 1: Study

Xenical was ingested t.i.d. by two middle aged healthy male volunteers on a normal average mixed diet. Both individuals frequently experienced one or more of the above mentioned unpleasant gastrointestinal side effects. After 4 weeks on Xenical they started to ingest in addition to Xenical b.i.d.. cholestyramine containing sachets (4 g/meal) which were emptied into about 100 ml water, swirled and drunk during the meals. The side effects were immediately reduced in frequency and completely disappeared. After 2-4 weeks of combined intake together with Xenical, cholestyramine was discontinued. When treatment with Xenical alone was carried on the gastrointestinal adverse events reappeared.

Example 2: Orlistat Pharmaceutical Compositions

A)

Ingredient	Quantity mg/Capsule
Orlistat	120.00
Microcrystalline Cellulose (AVICEL PH-101)	93.60
Sodium Starch Glycolate (PRIMOJEL)	7.20
Sodium Lauryl Sulfate	7.20
Polyvinylpyrrolidone (Povidone (K-30))	12.00
Purified Water*	———
Talc	0.24
Total	240.24 mg

*Removed during processing

Procedure:

1. Blend orlistat, microcrystalline cellulose, and sodium starch glycolate in a suitable mixer.
2. Granulate with a solution of polyvinylpyrrolidone and sodium lauryl sulfate in purified water.
3. Pass the granulation through an extruder and pass the extrudate through a spheronizer to form pellets.
4. Dry the pellets at 30°C.
5. Add talc and mix.
6. Fill into hard gelatin capsules.

B)

Ingredient	Quantity mg/Capsule
Orlistat	60
Microcrystalline Cellulose	46.8
Sodium Starch Glycolate	3.6
Sodium Lauryl Sulfate	3.6
Polyvinylpyrrolidone	6.0
Purified Water*	———
Talc	0.12
Total	120.12 mg

*Removed during processing.

Procedure:

1. Blend orlistat, microcrystalline cellulose, and sodium starch glycolate in a suitable mixer.
2. Granulate with solution of polyvinylpyrrolidone and sodium lauryl sulfate in purified water.
3. Pass the granulation through an extruder and pass the extrudate through a spheronizer to form pellets.
4. Dry the pellets at 30°C.
5. Add talc and mix.

6. Fill into hard gelatin capsules.

C)

Ingredient	Quantity mg/Capsule	
Orlistat	60	120
Lactose	40	80
Microcrystalline Cellulose	60	120
Sodium Lauryl Sulfate	5.7	11.4
Sodium Starch Glycolate	20	40
Polyvinylpyrrolidone	10	20
Purified Water*	—	—
Talc	0.2	0.4
Total	195.9 mg	391.8 mg

*Removed during processing.

Procedure:

1. Blend orlistat, lactose, microcrystalline cellulose and sodium starch glycolate in a suitable mixer.
2. Granulate with a solution of polyvinylpyrollidone and sodium lauryl sulfate in purified water.
3. Pass the granulation through an extruder, and pass the extrudate through a spheronizer to form pellets.
4. Dry the pellets at 30°C.
5. Add talc and mix.
6. Fill into hard gelatin capsules.

Example 3: Bile Acid Sequestrant Pharmaceutical Compositions

Ingredient	Quantity mg/Capsule
Cholestyramine	4 g
Silicium Dioxide	0.495 g
Aspartame	0.05 g
β-carotene	0.001 g
Purified Water*	———
Total	4.5 g

*Removed during processing

Procedure:

1. Blend colestyramine, and silicium dioxide in a suitable mixer.
2. Granulate with a solution /colloidal suspension of Aspartame and beta carotene in purified water.
3. Pass the granulation through an sieve.
4. Dry the granules at 60°C..
5. Pass the dry granulation through an sieve
6. Fill into sachets.

Example 4: Bile Acid Sequestrant Pharmaceutical Compositions

Ingredient	Quantity mg/Capsule
Cholestyramine	4 g
Silicium Dioxide	0.5g
Saccharose	3 g
β-carotene	0.001 g
Purified Water*	———
Total	7.5 g

*Removed during processing

Procedure:

1. Blend colestyramine, silicium dioxide, and saccharose in a suitable mixer.
2. Granulate with a solution /colloidal suspension of Aspartame and beta carotene in purified water.
3. Pass the granulation through an sieve.
4. Dry the granules at 60°C.
5. Pass the dry granulation through an sieve
6. Fill into sachets.

Example 5: Bile Acid Sequestrant Pharmaceutical Compositions

Ingredient	Quantity mg/Capsule
Cholestyramine	4 g
Aspartame	0.5 g
β-carotene	0.001 g
Purified Water*	———
Total	4.05 g

*Removed during processing

Procedure:

1. Fill colestyramine in a suitable mixer.
2. Granulate with a solution /colloidal suspension of Aspartame and beta carotene in purified wa
3. Pass the granulation through an sieve.
4. Dry the granules at 60°C..
5. Pass the dry granulation through an sieve
6. Fill into sachets.

Example 6: Orlistat/Bile Acid Sequestrant Pharmaceutical Compositions

Ingredient	Quantity mg/Capsule
Orlistat	120 mg
Maltodextrinum	740 mg
Cholestyramine	4000 mg
Aspartame	440 mg
Purified Water*	———
Total	5.3 g

*Removed during processing

Procedure:

1. Melt Orlistat in a mixer and add Maltodextrin.
2. Mix until solidification at room temperature (first part)
3. Blend colestyramine, and silicium dioxide in a suitable mixer.
4. Granulate with a solution /colloidal suspension of Aspartame and beta carotene in purified water.
5. Pass the granulation through an sieve.
6. Dry the granules at 60°C..
7. Pass the dry granulation through an sieve (second part)
8. Blend both parts in a mixer

9. Fill into sachets.

Example 7: Orlistat/Bile Acid Sequestrant Pharmaceutical Compositions

Ingredient	Quantity mg/Capsule
Orlistat	120 mg
Microcrystalline Cellulose	240 mg
Sodium Starch Glycolate	60 mg
Sodium Lauryl Sulfate	30 mg
Crospovidone	50 mg
Colestyramine	4000 mg
Aspartame	200 mg
Purified Water*	———
Total	5.2 g

*Removed during processing

Procedure:

1. Blend colestyramine, Orlistat, Avicel, Sodium Starch glycolate and Crospovidone in a suitable mixer.
2. Granulate with a solution /colloidal suspension of Sodium Lauryl Sulfate, Aspartame in purified water.
3. Pass the granulation through an sieve.
4. Dry the granules at 30°C.
5. Pass the dry granulation through a sieve
6. Fill into sachets.

CLAIMS

1. A pharmaceutical composition comprising a lipase inhibitor and a pharmaceutically acceptable bile acid sequestrant in conjunction with a pharmaceutically acceptable diluent or carrier.

2. The pharmaceutical composition according to claim 1, wherein the lipase inhibitor is orlistat.

3. The composition according to any preceding claim wherein the pharmaceutically acceptable bile acid sequestrant is selected from the group consisting of cholestyramine, colestipol, colesevelam, GT102-279, sevelamer, cellulose and dextran derivatives, starch and starch derivatives and pharmaceutically acceptable salts thereof.

4. The composition according to any of claims 1 to 3, wherein the bile acid sequestrant is a cellulose or dextran derivative.

5. The composition according to any of claims 1 to 4, wherein the cellulose or dextran derivative is selected from the group consisting of DEAE-cellulose, guanidinoethylcellulose, and DEAE-Sephadex.

6. The composition according to any of claims 1 to 3, wherein the starch derivative is selected from the group consisting of β- or γ-cyclodextrin, degraded starch (Dansil), hydrophobic starch, amylose, starch-diethylaminoethylether and starch-2-hydroxyethylether.

7. The composition according to claim 6, wherein the starch derivative is selected from β- or γ- cyclodextrin.

8. The composition according to any of claims 1 to 3, wherein the bile acid sequestrant is selected from the group consisting of cholestyramine, colestipol, colesevelam, GT102-279, sevelamer, cellulose, DEAE-cellulose, guanidinoethylcellulose, and DEAE-Sephadex, starch, β- or γ-cyclodextrin.

9. The composition according to claim 8, wherein the bile acid sequestrant is selected form the group consisting of cholestyramine, colestipol, colesevelam, GT102-279, sevelamer, DEAE-cellulose, and β- or γ-cyclodextrin.

10. The composition according to claims 8 and 9, wherein the bile acid sequestrant is selected from the group consisting of cholestyramine, colestipol, sevelamer, DEAE-cellulose, and β- or γ-cyclodextrin.

11. The composition according to any of claims 8 to 10, wherein the bile acid sequestrant is selected from the group consisting of cholestyramine, colestipol, and sevelamer.

12. The composition according to any of claims 8 to 11, wherein the bile acid sequestrant is cholestyramine.

13. The composition according to any of claims 8 to 11, wherein the bile acid sequestrant is colestipol.

14. The composition according to any of claims 8 to 11, wherein the bile acid sequestrant is sevelamer.

15. The composition according to any preceding claim, comprising a) about 5 to about 1000 mg lipase inhibitor and b) about 0.1 to about 20 g bile acid sequestrant.

16. The composition according to any preceding claim, wherein the pharmaceutically acceptable diluent or carrier is selected from the group consisting of fillers, sugars and/or sugar alcohols, surfactants, disintegrants, polymers, lubricants, flowability enhancers , sweeteners, and colorants.

17. The composition according to any preceding claim, comprising
a) about 5 to about 1000 mg lipase inhibitor;
b) about 0.1 to about 20 g bile acid sequestrant; and
optionally pharmaceutically acceptable excipients selected from the group of about 0.1 to about 10 g fillers, sugars and/or sugar alcohols, about 0.05 to about 3.0 g surfactants, about 0.05 to about 2.0 g disintegrants, about 0.02 to about 2.0 polymers, about 0.001 to about 1.0 g lubricants, about 0.1 to about 5.0 g flowability enhancers , about 0.01 to about 4.0 g sweeteners, and about 0.001 to about 0.5 g colorants.

18. The composition according to claim 17, wherein the lipase inhibitor is orlistat.

19. The compositions according to any preceding claim comprising about 10 to about 500 mg lipase inhibitor.

20. The composition according any preceding claim comprising about 20 to about 100 mg lipase inhibitor.

21. The composition according to any preceding claim comprising about 10 to about 360 mg orlistat.

22. The composition according to any preceding claim comprising about 30 to about 120 mg orlistat.

23. The composition according to any preceding claim comprising about 40 to about 80 mg orlistat.

24. The composition according to any preceding claim comprising about 0.5 to about 10 g bile acid sequestrant.

25. The composition according to any preceding claim comprising about 1 to about 5 g bile acid sequestrant.

26. The compositions of any of claims 1 to 25 for use in the treatment and prevention of obesity.

27. A process for preparing a composition according to any of claims 1 to 25, comprising mixing a lipase inhibitor with a bile acid sequestrant and one or more pharmaceutically acceptable diluent and/or carrier.

28. Kit for treatment of obesity, said kit comprising a first component which is a lipase inhibitor and b) a second component which is a bile acid sequestrant in suitable oral unit dosage forms.

29. The use of a composition according to any of claims 1 to 25 in the manufacture of medicaments useful for the treatment and prevention of obesity.

30. The use of a lipase inhibitor as defined in any of claims 1 to 25 in the manufacture of a medicament for the treatment and prevention of obesity in a

patient who is also receiving treatment with a bile acid sequestrant as defined in any of claims 1 to 25.

31. The use according to claim 30 for simultaneous, separate or sequential use for the treatment and prevention of obesity.

32. A method of treatment of obesity in a human in need of such treatment which comprises administration to the human of a therapeutically effective amount of a lipase inhibitor and a therapeutically effective amount of a bile acid sequestrant as defined in any of claims 1 to 25.

33. The method according to claim 32 for the simultaneous, separate or sequential administration.

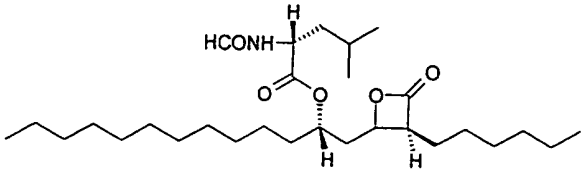
34. A lipase inhibitor and a bile acid sequestrant as defined in claims 1 to 25 for simultaneous, separate or sequential use for the treatment and prevention of obesity.

35. A lipase inhibitor and a bile acid sequestrant as defined in claims 1 to 25 as a combined preparation for simultaneous, separate or sequential use for the treatment and prevention of obesity.

36. The invention as hereinbefore described.

ABSTRACT

The present invention relates to pharmaceutical combinations, compositions and methods for treating obesity. More particularly, the invention relates to a combination or composition comprising a lipase inhibitor, preferably a compound of formula I (orlistat),



(I)

a pharmaceutically acceptable bile acid sequestrant thereof in conjunction with at least one pharmaceutically acceptable diluent or carrier.

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